A new era of quality control in multiple-breath washout measurements: an automated, model-based approach quantifies effects on the primary outcome LCI

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Nitrogen multiple-breath washout (N_2MBW) is a sensitive method for assessing ventilation inhomogeneity. However, **irregular behaviors during the measurement are frequent**, particularly among young and ill patients, and can lead to large variability and biased outcomes. Irregular behaviors include irregular breathing, variation in end-expiratory lung volume, and leaks. **Quality control (QC) is thus an important step** in ensuring the correct interpretation of MBW tests but QC by experts is time-consuming, technically demanding, and subjective.

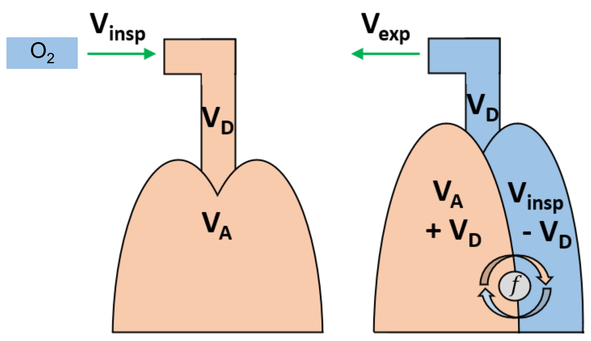
Aim: Presentation, application and validation of the novel automated QC on a set of N2MBW measurements of children with cystic fibrosis and comparison to manual quality control by experts.

Methods: Lung model for automated QC

A two-compartment lung model composed of alveolar Volume V_A, dead-space volume V_D and efficiency f was used to calculate the main outcome, the lung clearance index (**LCI**).
The model calculation for each washout breath is illustrated below:

Before inspiration N_2 is contained in volume $V_A + V_D$

O_2 is inspired (blue), before expiration N_2 is contained in volume $V_A + V_{insp}$



Concentration N_{2-new} of nitrogen after inspiration of volume V_{insp} of oxygen is given by

$$N_{2-new} = N_2 * \left(\frac{V_A + V_D}{V_A + V_{insp}}\right)^f$$

Efficiency of N_2 dilution is modeled by f.

Model parameters V_A , V_D, f were estimated for each N_2-MBW measurement.

This model calculation was performed repeatedly for each measurement individually with and without different irregular behaviors to determine the effect of each irregularity on LCI.

The QC method estimated the effect of the following irregular behaviors:
- variation in tidal volume $\mathbf{V_T}$ and average $\mathbf{V_T}$ size
- variation in end expiratory lung volume (**EELV)**
- variation of breath size at end of test (**ET**)
- leaks or trapped gas
- overflow (too strong inspiration flow)

A measurement was rejected by our QC method if irregular behavior led to an estimated effect on LCI exceeding a threshold of 15%.

Application and validation of automated QC:
1. We validated the automated QC algorithm against a first data set of 2471 measurements from 87 children with cystic fibrosis (CF) by estimation of irregularity causing rejection.
2. Association of within-visit variability with estimated variability was calculated for this same data.
3. On a second set of 50 measurements in healthy children automated QC was compared to QC ratings by experts.

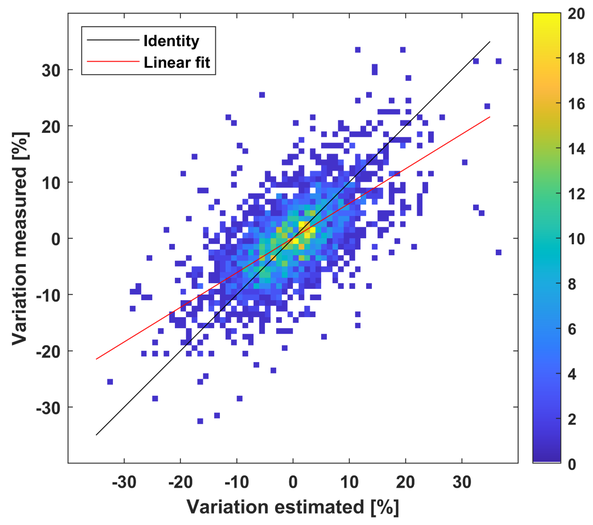
Automated QC: rejection ratio and irregularity

2471 measurements of 87 children with CF aged 3-18 years	
Evaluated	all
Accepted	76%
Rejected	24%

Individual effects of quality control tests for irregular behavior: The table shows how often each test showed a result that exceeded the acceptability threshold of 15%, as well as how often it was the largest source of error for the measurement.
ET: End of test, **EELV**: End-expiratory lung volume, $\mathbf{V_T}$: Tidal volume.

EFFECT NAME	EXCEEDS THRESHOLD [%]	LARGEST ERROR [%]
LEAK, TRAPPED GAS	9.6	30.7
ET BREATH SIZE VARIATION	4.3	19.2
EELV VARIATION	3.8	22.9
SIGNAL RESYNCHRONIZATION	2.3	15.9
V_T SIZE	1.7	5.9
BREATH DETECTION	0.7	1.6
V_T VARIATION	0.2	3.8
OVERFLOW	0.1	0.0

Association of per-visit variation of LCI with estimated variation



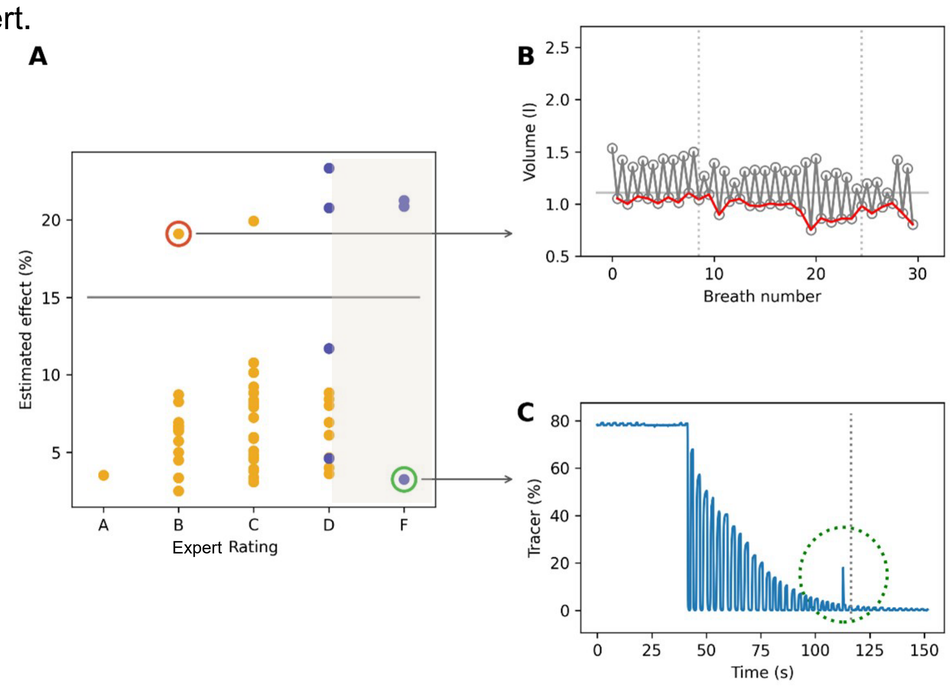
Scatter plot of 2471 measurements, with at least 3 per visit.

- On the y-axis is the measured deviation from the per-visit mean LCI.
- The x-axis shows the deviation from per-visit mean of the aggregation of all estimated effects.
- Color represents number of measurements.

The aggregated effects of automated QC explain 45% of the observed variation.

Automated versus expert QC

Automated QC can quantify effects, which are difficult to quantify for the expert.



A: Effects estimated by automated QC versus expert ratings (A: good to F: bad) for a set of 50 measurements in healthy children. Yellow dots represent measurements accepted by expert, blue dots rejected ones. Horizontal line (15%) is acceptance threshold for automated QC.
B: Illustration of red circled sample: changes in end-expiratory lung volume (EELV) result in an estimated impact of almost 20% in LCI. Lung volume of this measurement (grey line) together with the EELV (red line).
C: Tracer concentration for the green circled measurement in (A). A leak (marked by dotted circle) during expiration towards washout end (dotted line) is clearly visible, resulting in an expert QC F-rating. The volume of tracer gas corresponding to the leak is small, and visually, the end-expiratory tracer concentration follows the expected exponential decrease, unaffected by the leak. Computation indicates that the impact of this leak on LCI and FRC is below 5%.

Conclusion

- Our novel approach to QC uses a fast, reproducible method to provide detailed insights into measured variation of LCI related to the patient's irregular behavior during the measurement.
- Rather than a simple accept/reject QC output, our method quantifies irregularities as an expected difference in LCI.

Preprint available on medRxiv